



ELSEVIER

BIAM  
British Infection Association

www.elsevierhealth.com/journals/jinf

## REVIEW

# ***Aspergillus* meningitis: A rare clinical manifestation of central nervous system aspergillosis. Case report and review of 92 cases**

Q3 Spinello Antinori <sup>a,\*</sup>, Mario Corbellino <sup>a</sup>, Luca Meroni <sup>a</sup>, Federico Resta <sup>b</sup>,  
Salvatore Sollima <sup>a</sup>, Massimo Tonolini <sup>b</sup>, Anna Maria Tortorano <sup>c</sup>,  
Laura Milazzo <sup>a</sup>, Lorenzo Bello <sup>d</sup>, Elisa Furfaro <sup>e</sup>, Massimo Galli <sup>a</sup>,  
Claudio Viscoli <sup>e</sup>

<sup>a</sup> Department of Biomedical and Clinical Sciences Luigi Sacco, Università Di Milano, Milano, Italy

<sup>b</sup> Radiology Unit, L Sacco Hospital, Milano, Italy

<sup>c</sup> Department of Biomedical Sciences for Health, Università Di Milano, Milano, Italy

<sup>d</sup> Department of Medical Biotechnology and Translational Medicine, Università Di Milano, Milano, Italy

<sup>e</sup> Division of Infectious Diseases, San Martino Hospital, University of Genova, Genova, Italy

Accepted 5 November 2012

Available online ■ ■ ■

**KEYWORDS**

*Aspergillus* meningitis;  
Galactomannan  
antigen;  
Diagnosis;  
Therapy

**Summary** *Objectives:* To describe the pathogenesis, clinical presentation, cerebrospinal fluid findings and outcome of *Aspergillus* meningitis, meningoencephalitis and arachnoiditis.

*Methods:* A case of *Aspergillus* meningitis is described. A comprehensive review of the English-language literature was conducted to identify all reported cases of *Aspergillus* meningitis described between January 1973 and December 2011.

*Results:* Ninety-three cases (including the one described herein) of *Aspergillus* meningitis were identified. Fifty-two (55.9%) were in individuals without any predisposing factor or known causes of immunosuppression. Acute and chronic meningitis was diagnosed in 65.6% of patients and meningoencephalitis in 24.7% of them with the remaining presenting with spinal arachnoiditis and ventriculitis. Cerebrospinal fluid cultures for *Aspergillus* spp. were positive in about 31% of cases and the galactomannan antigen test in 87%. Diagnosis during life was achieved in 52 patients (55.9%) with a case fatality rate of 50%. The overall case fatality rate was 72.1%.

\* Corresponding author. Department of Biomedical and Clinical Sciences Luigi Sacco, Università degli Studi di Milano, Via GB Grassi 74, 20157 Milano, Italy. Tel.: +39 0250319765; fax: +39 0250319758.

E-mail address: [spinello.antinori@unimi.it](mailto:spinello.antinori@unimi.it) (S. Antinori).

**Conclusions:** *Aspergillus* meningitis may occur in both immunocompetent and immunocompromised patients and run an acute or chronic course. The findings of this systematic review extend the information on this life-threatening infection and could assist physicians in achieving an improved outcome.

© 2012 The British Infection Association. Published by Elsevier Ltd. All rights reserved.

Central nervous system (CNS) infections are well recognized manifestations of disseminated aspergillosis observed in about 10% of immunocompromised patients and with mortality rates greater than 90%.<sup>1,2</sup> By contrast, *Aspergillus* meningitis is a more seldomly encountered clinical entity and it is found more frequently in immunocompetent rather than in immunocompromised hosts.<sup>3–8</sup> Information about *Aspergillus* meningitis is limited and sparse and to our knowledge no review on this topic has been published so far. We present here a case of *Aspergillus* meningitis, along with a review of published cases since 1973.

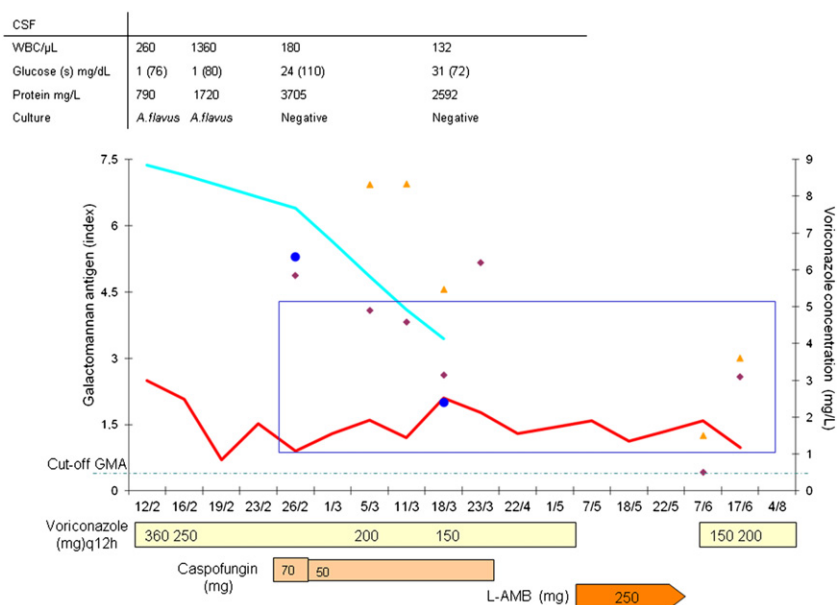
## Methods

Case reports of *Aspergillus* meningitis, meningoencephalitis, arachnoiditis and ventriculitis as well as series of CNS aspergillosis were identified through a search of PubMed and Scopus databases of the English literature, and the reference lists were reviewed for additional cases. Research was conducted from the year 1973 through 2011. Used research terms included “*Aspergillus* meningitis”, “cerebral aspergillosis”, “central nervous system aspergillosis”, “*Aspergillus* arachnoiditis”, “mycotic meningitis”. For the purpose of this review a case of meningitis or meningoencephalitis caused by *Aspergillus* spp. was defined during life as follows: 1) a cerebrospinal culture positive for *Aspergillus* spp. together with a meningeal or encephalic syndrome; 2) the presence of galactomannan antigen or *Aspergillus* DNA detected by polymerase chain reaction (PCR) test in the CSF, together with a meningeal syndrome. *Post-mortem* diagnoses of *Aspergillus* meningitis were included if the autopsy clearly indicated involvement of the meninges or a picture of meningitis with microscopy identification of *Aspergillus* hyphae or a positive *Aspergillus* culture. When inflammation involved the spinal leptomeninges the case was classified as spinal arachnoiditis. Patients were considered immunocompromised if the following conditions were met: 1) HIV/AIDS infection; 2) solid organ transplantation; 3) hematologic diseases with or without bone marrow transplantation; 4) autoimmune diseases treated with steroids or other immunosuppressive drugs; 5) diabetes mellitus; 6) any other condition treated with corticosteroids or immunosuppressive drugs.

## Case report

A 34-year-old man was referred to our Infectious Diseases ward on February 9, 2010 from a Neurosurgery Unit where a diagnosis of *Aspergillus* meningitis had been made (Fig. 1). The clinical history was notable for heroin intravenous drug abuse, high alcohol intake, untreated chronic hepatitis C and methadone maintenance therapy (50 mg/

day). One month before he was admitted to the Internal Medicine ward of another Hospital to investigate the nature of low back pain, headache and low grade fever (37.5 °C) that had appeared 1 month earlier. Magnetic resonance imaging (MRI) of the brain was negative for parenchymal and meningeal lesions. On the contrary, MRI of the lumbar spine showed abnormal contrast enhancement into the spinal canal between L4 and S1 suggesting an intradural mass lesion conditioning a traction effect on the roots of the *cauda equina*. A color-doppler echocardiogram showed only a mild mitral regurgitation. Blood and urine cultures were negative as well as a serologic test for HIV. Cerebrospinal fluid (CSF) analysis performed on February 9 is shown in Fig. 1. Gram and Ziehl-Neelsen stains, as well as bacterial and mycobacterial cultures, were negative as was the search for bacterial and *Cryptococcus neoformans* antigens. Cerebrospinal culture grew *Aspergillus flavus* that was susceptible to amphotericin B, voriconazole, posaconazole, itraconazole and caspofungin. *Aspergillus* galactomannan antigen-GM (Platelia *Aspergillus*, Sanofi Diagnostics Pasteur, Marne-La Coquette, France) was detected both in the CSF and blood with a higher index value in the former (respectively, 7.4 and 2.5). Upon admission to our ward (February 12), the patient had fever (38.5 °C) was alert and complained of frontal headache and photophobia, without neck stiffness. Intravenous treatment with voriconazole was started (6 mg/kg every 12 h (q12h) as loading dose, followed by 4 mg/kg q12h) together with ceftriaxone (2 g q12). Two weeks later, a control brain and spinal MRI showed meningeal enhancement with cysternal distribution especially in the pre-pontine area around the basilar artery, together with endocanal pathologic enhancement between L4 and S2 (Fig. 3a and b). A concomitant CSF analysis showed a reduction of WBCs (180/μL, 61% PMNs), improvement of glucose levels (24 mg/dL, serum 110 mg/dL) and a striking increase of protein level (3705 mg/dL), whereas, at this time point, CSF culture turned negative. The GM index was 6.36 in the CSF and 0.9 in the peripheral blood. Because of persistent fever, headache and worsening of the radiological picture, caspofungin (70 mg loading dose, 50 mg maintenance dose) was added to the antifungal regimen with discontinuation of the antibiotic therapy. Voriconazole blood and CSF trough concentrations obtained after 2 weeks of therapy were similar (5.85 and 5.86 mg/L, respectively). Therapeutic drug monitoring was arranged 6 and 10 days later and it showed toxic concentrations of the drug that prompted dosage adjustments despite the absence of any clinical or biochemical signs of voriconazole toxicity. Another CSF examination performed on March 18, which disclosed an improvement of all parameters (Fig. 1). Repeated MRI of the brain and spine (March, 17) showed the reduction of the pial and cysternal contrast enhancement but a progression of the endocanal inflammation now involving the



**Figure 1** Medication history, clinical course and kinetic of *Aspergillus* antigen in CSF of our case of *Aspergillus flavus* meningitis. The dotted line represents the cut-off value of GM. The light blue line is the index on CSF and the red line on plasma. The blue circle represents the CSF levels of voriconazole. The purple diamond and the yellow triangle are respectively the down and peak plasma levels of voriconazole. The blue rectangle denotes the range of expected therapeutic levels of voriconazole.

segments L3 to S2. After a new evaluation by the neurosurgery consultant, who deemed any procedure unfeasible, the patient was discharged after having received 38 days of voriconazole therapy (total cumulative dosage: 21,200 mg) and one month of caspofungin (total cumulative dosage: 1520 mg). The patient was left on maintenance therapy with oral voriconazole at a dosage of 150 mg q12 due to raised ALT levels (199 U/L), the appearance of visual disturbances and persistently elevated trough voriconazole concentrations (6.2 mg/L). At the end of April, the patient was readmitted to our hospital ward because of persistent abnormal liver function test results and visual disturbances that required discontinuation of voriconazole and its substitution with intravenous liposomal amphotericin B (L-

AMB, 250 mg/day). He complained of persistent low back pain that was irradiated to both the lower extremities with preserved deep tendon and superficial reflexes. Repeated attempts to obtain CSF samples by lumbar puncture were unsuccessful. Nerve conduction and electromyography studies showed mild sensorimotor bilateral demyelinating polyneuropathy. A new MRI of the brain and spine (performed on May, 17) was substantially unchanged. During the 30-day therapy with L-AMB, GM was evaluated weekly and showed values ranging from 0.9 to 1.59. Because of the patient's drug addiction history, it was decided to resume oral voriconazole therapy since the positioning of a permanent intravenous device for L-AMB infusion on an outpatient basis was judged risky. A dosage



**Figure 2** Sagittal and coronal T1-weighted gadolinium-enhanced magnetic resonance scan of the brain of our patient with *Aspergillus flavus* meningitis showing contrast impregnation along the basilar artery in the prepontine cistern.





**Figure 3** Sagittal T2 (a) and gadolinium enhanced T1-weighted (T1W) (b) MRI demonstrate pathologic enhancement and endocanalicular pathologic tissue of the L4-S2 tract.

of 150 mg every 12 h was started on June 9, showing after a week trough and peak concentrations of 3.4 and 3.6 mg/L, respectively. A new MRI of the brain and spine was performed on August 4, that demonstrated a reduction of pial enhancement along the cervical tract, the *conus medullaris* and *cauda equina* with a only a mild volumetric reduction of the endocanalicular lumbar abscess. Clinically, the patient was well oriented with a positive bilateral *Lasègue* sign at the neurologic examination. He was discharged and subsequently lost to follow-up (Fig. 2).

## Results

A detailed, chronologically ordered summary of 93 cases of *Aspergillus* meningitis, chronic meningitis/pachymeningitis, meningoencephalitis, arachnoiditis and ventriculitis including the one presented herein (case 46) is shown in Table 1. There were 46 women (50%) and 46 men, with a median age of 37 years (range 3–75 years). Diagnosis was made during life in 52 patients (55.9%) and at autopsy in 41 patients. A diagnosis was obtained more frequently during life among immunocompetent patients (69%) in comparison with immunocompromised individuals (39%) (Table 2).

In almost half of the cases ( $n = 44$ ) *Aspergillus* was identified by histology or culture without speciation; all other infections were caused by *A. fumigatus* ( $n = 34$ ), *A. flavus* ( $n = 8$ ) and *A. terreus* ( $n = 3$ ) while *A. oryzae*, *A. granulatus* and *A. candidus* were identified in one case each. Forty-one patients were considered immunocompromised hosts (5 AIDS patients; 3 with autoimmune diseases treated with steroids; 9 solid organ transplant recipients; 10 hematologic patients undergoing chemotherapy or bone marrow transplantation; 5 subjects under steroid therapy for chronic obstructive pulmonary disease (COPD), and Severe Acute Respiratory Syndrome; 7 patients with diabetes and, finally, 1 each with Cushing's disease and sarcoidosis). In the fifty-two patients without classic risk factors for invasive aspergillosis, central nervous system involvement was presumed to be the result of: direct extension of *Aspergillus* from the orbit, ear or paranasal sinuses in 6 patients (11.5%);

iatrogenic direct inoculation of *Aspergillus* through spinal anesthesia (13 patients, 25%), neurosurgery (13 patients, 25%) or epidural steroid injections (1 patient). In six intravenous drug abusers (11.5%) the infection was probably acquired by the hematogenous route. Among the remaining subjects, no predisposing factor could be identified in six patients while one patient each were notable for the presence of the following: pregnancy, alcohol abuse, fungal endocarditis and near drowning. The most common syndrome was acute meningitis which was observed in 46 patients, followed by meningoencephalitis ( $n = 23$ ). A chronic course of meningitis was observed in 15 patients; five patients showed a picture of spinal arachnoiditis (in 1 case with associated meningitis), and 4 ventriculitis (Table 2). An acute course characterized by rapid deterioration of the clinical picture usually ending with death was observed among immunocompromised hosts and in patients who had direct inoculation of the fungus into the cerebrospinal fluid or the subarachnoid space. By contrast, a sub-acute or chronic form of meningitis going unrecognized for several weeks and sometimes displaying a relapsing character was the most frequent presentation among immunocompetent patients, intravenous drug abusers and patients with diabetes. However, the latter clinical picture was also observed among several patients who had undergone neurosurgery.

Cerebrospinal fluid culture was positive for *Aspergillus* spp. in 31% of cases with a slightly higher prevalence among immunocompetent (36.9%), as opposed to immunocompromised hosts (18.2%) (Table 2). In nine patients, *Aspergillus* spp. was cultured from CSF only after repeated attempts (median number of lumbar punctures: 4, range 3–9). Antigen-based assays were employed in fifteen patients: GM antigen by use of the Platelia Elisa in 10 patients, with an unspecified assay in 2 patients, with Pastorex assay in 1 patient and 1,3- $\beta$ -D-glucan in 2 individuals. GM antigen was detected in CSF specimens of 6 out of 8 immunocompetent patients and in all immunocompromised hosts in whom it was assessed (7/7, 100%) with an overall sensitivity of 86.7%. The median CSF GM index was 6.58 (range 2.2–578).

Serum GM was concomitantly measured in 8 cases and turned positive in 3. In 3 patients, CSF GM was serially determined (3–10, median 7), showing a good correlation

**Table 1** Characteristics of patients with *Aspergillus* meningitis.

Author, year [Reference]	Age/sex	Risk factor/Underlying disease	Sign and symptoms (time duration)/ Time from TX	Syndrome	Diagnosis/methods	CSF characteristics	<i>Aspergillus</i> species	CSF Ag GMN (method)	Antifungal treatment (time duration)	Outcome
Meningitis										
Atkinson & Israel, 1973 <sup>9</sup>	27/M	None/Sarcoidosis	Headache, blurred vision	Meningitis	L/CSF	WBC 144/μL (PMNs 10%)	<i>Aspergillus fumigatus</i> (CSF)	NA	5-FLU (3 months)	Alive 2 years after stopping antifungal therapy
Feely et al., 1977 <sup>10</sup>	57/F	Neurosurgery (Trans- sphenoidal Yttrium <sup>90</sup> implant)/Acromegaly	Meningeal signs, left hemiparesis/11 months	Meningitis	Pm/Autopsy (purulent basal leptomeningitis + multiple infarcts)	WBC 138/μL (PMNs 96%); proteins 850 mg/L	<i>Aspergillus</i> spp. (autopsy culture)	NA	None	Death after 1 day
	37/M	Neurosurgery (Trans- sphenoidal Yttrium <sup>90</sup> implant)/Diabetic retinopathy	Fever, stiff neck, headache, blurred vision/9 months	Meningitis	L/Biopsy (tissue adherent to the screws)	WBC 8800/μL (PMNs 90%); protein 330 mg/L	<i>Aspergillus</i> spp. (biopsy)	NA	AMFB (NR)+ removal of implant	Alive
Mohandas et al., 1978 <sup>11</sup>	38/M	Neurosurgery/maxillary sinusitis	Meningeal irritation, coma/6 days post- operatively	Meningitis	L/Surgery of fungal granuloma	WBC 100/μL (PMNs 0%); glucose 35 mg/dL; protein 1160 mg/L	<i>Aspergillus</i> spp. (biopsy)	NA	AMFB (7 days) ev + intrathecal (1 day)	Death after 7 days
Aung et al., 1979 <sup>12</sup>	22/F	Pregnancy/None	Headache, retrobulbar pain, blurred vision, ophthalmoplegia (22 days after delivery)	Meningitis	L/Biopsy leptomeninges	ND	<i>Aspergillus</i> spp. (biopsy)	NA	Antifungal drugs (not mentioned)	Death after 1 month
Beal et al., 1982 <sup>13</sup>	47/F	None/Sphenoid sinusitis	Frontal headache (5 months); nuchal rigidity, fever, hydrocephalus	Meningitis	L/biopsy sinus	WBC 120/μL (PMNs 63%); glucose 25 mg/dL; protein 620 mg/L	<i>Aspergillus</i> spp. (sinus biopsy)	NA	AMFB (NR)	Alive 2 years later
	22/F	Neurosurgery/ Medullo-blastoma	Fever (38.8 °C), severe headache, meningismus 12 days after neurosurgery	Meningitis	L/CSF; Autopsy (basilar <i>Aspergillus</i> meningitis with exudate in the subarachnoid space of spinal cord)	WBC 2650/μL (PMNs 10%); glucose 26 mg/dL; protein 1750 mg/L	<i>Aspergillus</i> spp. (CSF culture after multiple attempts)	NA	AMFB (3 days)	Death after 20 days
Diendogh et al., 1983 <sup>14</sup>	60/M	Neurosurgery (Trans- sphenoidal Yttrium <sup>90</sup> implant)/Diabetic retinopathy	Drowsy, disoriented in time and space, neck stiffness, positive Kernig sign	Meningitis	PM/Autopsy (meningitis; necrotizing vasculitis (pons); fungal invasion of basilar and middle cerebral arteries)	WBC 323/μL (PMNs 60%)	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death after 2 weeks
Walsh et al., 1985 <sup>8</sup>	64/F	Steroid treatment/ Cushing syndrome	Meningismus, headache, hemiparesis	Meningitis	Pm/Autopsy : mycotic <i>Aspergillus</i> aneurism & subarachnoid hemorrhage	WBC 15/μL (PMNs 0%); glucose 90 mg/dL; protein 1450 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death after 9 days

(continued on next page)

Hajjar et al., 1987 <sup>15</sup>	28/M	Neurosurgery/Acoustic neuroma	NR/9 days	Meningitis	L/Wound culture	NR	<i>Aspergillus fumigatus</i> (wound culture)	NA	AMFB + 5-FLU (2 months)	Death after 2 months
Asnis et al., 1988 <sup>16</sup>	44/M	None/AIDS	Confusion, generalized seizures	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> eptomeningites)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	AMFB (20 days)	Death
Carrazana et al., 1991 <sup>17</sup>	44/M	None/AIDS; sphenoid sinusitis	Headache, fever, nausea, ataxia, hemiparesis, seizures	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> meningeal infiltration; thrombosis of basilar artery)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death
Komatsu et al., 1991 <sup>18</sup>	61/F	Neurosurgery/Rathke's cleft cyst	High fever and meningeal signs/12 days after surgery	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> meningitis & mycotic aneurism, subarachnoid hemorrhage)	WBC 881/μL (PMNs 70%); glucose 46 mg/dL; protein 540 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	ND	Death after 23 days
Lammens et al., 1992 <sup>19</sup>	39/F	Immunosuppressive therapy/SLE	Headache (1 month), fever (39.5 °C), neck stiffness, Horner syndrome	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> basal meningitis & subarachnoid hemorrhage)	WBC 3750/μL (PMNs 84%); glucose 32 mg/dL; protein 1000 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	None	Death after 15 days
Torre-Cisneros et al., 1993 <sup>20</sup>	31/F	Liver transplant/End stage liver disease	Seizure <sup>a</sup>	Meningitis	Pm/Autopsy (ischemic infarcts; leptomeningeal aspergillosis)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death
	21/F	Liver transplant/End stage liver disease	NR <sup>a</sup>	Meningitis	Pm/Autopsy (ischemic infarct; leptomeningeal aspergillosis)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death
	24/F	Liver transplant/End stage liver disease	Seizure <sup>a</sup>	Meningitis	Pm/Autopsy (acute leptomeningitis)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death
	38/M	Kidney transplant/End stage kidney disease	Seizure <sup>a</sup>	Meningitis	Pm/Autopsy (acute leptomeningitis; haemorrhagic infarcts)	NR	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death
Miaux et al., 1995 <sup>21</sup>	41/M	Bone marrow transplant; steroids therapy/CML	Fever (38 °C), hemiplegia/2 months	Meningitis	Pm/Autopsy (thickening and meningeal inflammation with haemorrhagic necrosis; lung & heart involvement)	WBC 2000/μL (PMNs 95%); protein 900 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death after 5 days
	39/F	Bone marrow transplant; steroids therapy/RAEB	Mental confusion/3.5 months	Meningitis	Pm/Autopsy (brain hemorrhagic necrosis; lung involvement)	WBC 2560/μL (PMNs 98%);	<i>Aspergillus</i> spp. (autopsy histology)	NA	NR	Death after 8 days
Adunsky et al., 1996 <sup>22</sup>	74/M	None/None	Fever (38.3°), stuporous, left hemiplegia, dysarthria (1 day)	Meningitis	L/CSF	WBC 2400/μL (PMNs 94%); glucose 10 mg/dL; protein 1500 mg/L	<i>Aspergillus flavus</i> (CSFNA culture)	NA	AMFB (few days)	Death after few days

Please cite this article in press as: Antinori S, et al., *Aspergillus meningitis: A rare clinical manifestation of central nervous system aspergillosis*. Case report and review of 92 cases, J Infect (2012), <http://dx.doi.org/10.1016/j.jinf.2012.11.003>

Darras-Joly et al., 1996 <sup>23</sup>	68/M	Neurosurgery/ Metastatic cancer	Allucinations, disorientation, hemyanopsia/5 months after surgery	Meningitis; extradural empyaema; abscesses	L/Surgery extraduralNR abscess	<i>Aspergillus fumigatus</i> Negative (NR) (extradural abscess)	AMFB (2 months) + itraconazole (2 months)	Death after 12 months	
	29/M	Neurosurgery/Acoustic neurinoma	Fever (38 °C), severe headache/3 days after surgery	Meningitis; abscess;	L/CSF	WBC 830/μL (PMNs 53%); glucose 48 (s CSF culture) 155) mg/dL; protein 830 mg/L	<i>Aspergillus fumigatus</i> Positive (NR)	L-AMB (5 weeks)+ 5-FLU (7 weeks); itraconazole (6 months)	Alive after 12 months
Monlun et al., 1997 <sup>24</sup>	75/F	Steroid therapy/ Asthma	Fever (38 °C); acute respiratory failure (22 days)	Meningitis	Pm/Autopsy (right haemorrhagic infarct with subcortical vessel invasion and meningeal diffusion by <i>Aspergillus</i> ; pulmonary involvement)	ND	<i>Aspergillus</i> spp. (autopsy histology)	AMFB (3 weeks)	Death 22 days later
Verweij et al., 1999 <sup>25</sup>	73/F	Mastoidectomy/ Otitis media	Fever (39 °C), headache, vomiting, drowsiness, meningismus/NR	Meningitis	L/CSF (sixth attempt)	WBC 2130/μL; glucose 27 mg/dL (47 mg/dL serum); protein 150 mg/L	<i>Aspergillus fumigatus</i> 10.4 (Platelia) (CSF culture, 6th attempt + PCR)	Itraconazole 1 week; AMFB (4weeks + AMFB intraventricular; voriconazole (9 weeks)	Alive 12 months after voriconazole discontinuation
Mariushi et al., 1999 <sup>26</sup>	43/F	None/None	Headache, neck stiffness (11 days), fever (37.6 °C), nausea, chills	Meningitis	L/CSF	WBC 329/μL (PMNS 0%); glucose 46 mg/dL; protein 500 mg/L	<i>Aspergillus</i> spp. (CSF culture, 5th attempt)	Fluconazole (2 years)	Alive after 2 years
Arabi, 2001 <sup>27</sup>	58/M	None/Maxillary sinusitis	Confusion, progressive unresponsiveness, 4th nerve palsy 8 days after pneumonia	Meningitis	L/Sinus aspirate/ Autopsy: <i>Aspergillus</i> ventriculitis, meningitis; focal encephalitis; pneumonia)	WBC 3500/μL (PMNs 91%); glucose 77 mg/dL(s 102); protein 3370 mg/L	<i>Aspergillus fumigatus</i> ND (sinus culture)	AMFB (3 weeks)	Death 20 days later
Nenoff et al., 2001 <sup>28</sup>	74/M	Ethoidectomy and orbitotomia (for <i>A.fumigatus</i> orbital and sinus infection)/ Diabetes mellitus;	Vomiting, nausea, exophthalmus, sommolent and disorientated/7 months	Meningitis	L/Biopsy (orbital apex)/Autopsy: <i>Aspergillus</i> meningitis, vasculitis internal carotid, mycotic aneurism with subarachnoid hemorrhages	NR	<i>Aspergillus fumigatus</i> 1:2 (Pastorex) (biopsy)	AMFB+ 5-FLU (few days)	Death 3 weeks after surgical procedure
Moling et al., 2002 <sup>29</sup>	24/M	Kidney transplant (reject); Hemodialysis + steroid therapy/ complement 4 deficiency	Fever (39 °C); confusion; disorientation; right motor hemi- syndrome (2 weeks)	Meningitis	L/CSF	WBC 3200/μL; glucose 4 mg/dL	<i>A.fumigatus</i> (CSF culture, 4th attempt + PCR)	Fluconazole (2 weeks); L-AMB (3 weeks); itraconazole (4 months)	Alive after 7 months; Death after 6 years <sup>b</sup>

(continued on next page)

869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930

Table 1 (continued)

Kleinschmidt-De Masters, 2002 <sup>30</sup>	40/F	Steroid therapy/ Wegener's granulomatosis	NR	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> acute and chronic basilar granulomatous meningitis; mycotic aneurism; lung, skin, heart involvement)	NR	<i>Aspergillus</i> spp. (autopsy histology)	ND	NR	Death after 68 days
	51/M	Chemotherapy/ Lymphoma	NR	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> basilar meningitis; thrombotic occlusion of arteries)	NR	<i>Aspergillus</i> spp. (autopsy histology)	ND	NR	Death after 4 days
Pandian et al., 2004 <sup>31</sup>	34/F	Spinal anaesthesia/ None	Fever, headache, vomiting <sup>c</sup>	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 640/ $\mu$ L (PMNs 76%); glucose 32 mg/dL; protein 3600 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death
	21/F	Spinal anaesthesia/ None	Fever, headache, vomiting <sup>c</sup>	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 678/ $\mu$ L (PMNs 65%); glucose 23 mg/dL; protein 3600 mg/dl	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death
	42/F	Spinal anaesthesia/ None	Fever, headache, vomiting <sup>c</sup>	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 240/ $\mu$ L (PMNs 68%); glucose 23 mg/dL; protein 2400 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death
	32/F	Spinal anaesthesia/ None	Fever, headache, vomiting <sup>c</sup>	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 345/ $\mu$ L (PMNs 76%); glucose 23 mg/dL; protein 1230 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Unknown
	24/F	Spinal anaesthesia/ None	Fever, headache, vomiting <sup>c</sup>	Meningitis	Pm/Autopsy ( <i>Aspergillus</i> meningitis; mycotic aneurism with subarachnoid hemorrhage)	WBC 435/ $\mu$ L (PMNs 96%); glucose 32 mg/dL; protein 4200 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	None	Death after 18 months
Larson Kolbe et al., 2007 <sup>32</sup>	51/F	Epidural steroid injections/COPD	Mental status changes; 3rd nerve palsy/2 months	Meningitis	L/Disc aspiration	NR	<i>Aspergillus fumigatus</i> (disc aspiration + psoas abscess culture)	ND	Caspofungin + oriconazole (4 months)	Death after 5 months
Gunaratne et al., 2007 <sup>33,78</sup>	26/F	Spinal anesthesia (Pregnancy)/None	Low grade fever; headache; nausea; vomiting 12 days after sa	Meningitis	Pm/Autopsy	WBC 302/ $\mu$ L (PMNs 99%); glucose 56 mg/dl (s 115 mg/dL) <sup>d</sup> ; protein 680 mg/L	<i>Aspergillus fumigatus</i> (autopsy culture)	ND	Fluconazole	Death after 4 weeks

931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992



1055	1078
1056	1079
1057	1080
1058	1081
1059	1082
1060	1083
1061	1084
1062	1085
1063	1086
1064	1087
1065	1088
1066	1089
1067	1090
1068	1091
1069	1092
1070	1093
1071	1094
1072	1095
1073	1096
1074	1097
1075	1098
1076	1099
1077	1100
1078	1101
1079	1102
1080	1103
1081	1104
1082	1105
1083	1106
1084	1107
1085	1108
1086	1109
1087	1110
1088	1111
1089	1112
1090	1113
1091	1114
1092	1115
1093	1116

Table 1 (continued)

Gordon et al., 1976 <sup>3,79</sup>	34/F	IVDA (heroin, cocaine)/none	Bifrontal headache, neck stiffness (weeks), low-grade fever	Chronic meningitis	L/CSF	WBC 2892/ $\mu$ L (PMNs 80%); glucose 16 (s 110) mg/dL; protein 990 mg/L;	<i>Aspergillus oryzae</i> (CSF culture, 7th attempt)	NA	AMFB+ 5-FLU (12 months)	Alive (6 year later; episode of bilateral necrotizing scleritis due to <i>A. oryzae</i> ) <sup>8</sup>
Mielke et al., 1981 <sup>38</sup>	58/F	Neurosurgery/Acromegaly	Severe headache (4 months), retro-orbital pain, blindness, ophthalmoplegia/10 months	Chronic meningitis	Pm/Autopsy (chronic basilar meningitis by <i>A. fumigatus</i> & <i>C. albicans</i> ; mycotic aneurism of the basilar artery with subarachnoid hemorrhage)	ND	<i>Aspergillus fumigatus</i> (autopsy culture)	NA	None	Death after 7 days
Weinstein et al., 1982 <sup>39</sup>	67/M	None/none	Retro-orbital and periorbital pain, vertigo (months); decrease eye vision; weakness; malaise	Chronic meningitis	L/biopsy sphenoid wing	WBC 88/ $\mu$ L (PMNs 6%); glucose 53 (s 97) mg/dL; protein 1130 mg/L	<i>Aspergillus fumigatus</i> (biopsy + culture sphenoid)	NA	AMFB + rifampicin (2 weeks)	Death after 18 days from surgery
Salaki et al., 1984 <sup>40</sup>	32/M	Steroid treatment/SLE	Fever (38 °C), frontal headache, lethargy (3 weeks), stiff neck, 6th nerve palsy	Chronic meningitis	L/CSF + spinal aspirate	WBC 1400/ $\mu$ L (92%); glucose 33 mg/dL; protein 1100 mg/L	<i>Aspergillus fumigatus</i> (CSF culture, 4th attempt)	NA	AMFB +5-FLU (NR)	Alive
Woods et al., 1990 <sup>41</sup>	44/M	None/AIDS	Headache, fever, nausea, vomiting, lethargy, slurred speech, severe back pain (4 months)	Chronic meningitis	Pm/Autopsy ( <i>Aspergillus</i> acute and chronic basilar meningitis; spinal arachnoiditis; pleural, brain, lumbar spinal cord involvement)	WBC 80/ $\mu$ L (PMNs 80%); glucose 19 mg/dL; protein 2000 mg/L	<i>Aspergillus fumigatus</i> (autopsy culture)	NA	None	Death after 18 days
Murai et al., 1992 <sup>42</sup>	59/F	None/Diabetes; Liver cirrhosis; Mondini's anomaly; otitis media	Headache; hearing loss; multiple nerve palsy (6th, 8th, 9th, 10th, 11th)	Chronic pachymeningitis	L/surgery maxillary sinus	WBC 7/ $\mu$ L; protein 660 mg/L	<i>Aspergillus flavus</i> (surgery culture)	NA	Miconazole (2 months); 5-FLU, fluconazole (1 month)	Alive after 4 months
Kurino et al., 1993 <sup>43</sup>	63/M	None/Diabetes; otitis media	Fever, headache, hyperesthesia of face, abducens palsy, deafness	Chronic meningitis	Pm/biopsy granuloma + autopsy	WBC 138/ $\mu$ L (PMNs 50%); glucose 87 mg/dL; protein 1007 mg/L	<i>Aspergillus</i> spp. (biopsy + autopsy)	NA	None	Death 30 days post-surgery
Mochizuki et al., 2000 <sup>44</sup>	75/M	None/Otitis media	Multiple cranial nerve palsy (2nd, 3rd, 4th), impaired vision (4 months)	Chronic pachymeningitis	L/Biopsy	NR	<i>Aspergillus flavus</i> (biopsy culture)	ND	Fluconazole (4 weeks); AMFB (4 months)+5-FLU (4 months); itraconazole (5 months)	Alive after 36 months
Moling et al., 2002 <sup>29</sup>	48/M	Alcohol abuse/None	Headache, fever, gait instability, apathy (5 months)	Chronic meningitis + ventriculitis + arachnoiditis	L/CSF	WBC 1880/ $\mu$ L; glucose 20 mg/dL	<i>Aspergillus candidus</i> group (CSF culture)	6.7 (s 1.7) (Platelia)	AMFB (1 week); voriconazole (10 days); itraconazole (10 months)	Alive after 24 months

1241	Kowacs et al., 2004 <sup>45</sup>	26/M	Near drowning/None	Fever (37.2 °C), mild meningismus (4 weeks)	Chronic meningitis	L/CSF	WBC 165/μL (PMNs 69%); glucose 64 mg/dL; protein 778 mg/L	<i>Aspergillus fumigatus</i> (CSF culture, 3rd attempt)	ND	Fluconazole (12 days); itraconazole + AMFB (44 days)	Death after 56 days
1242	Ismail et al., 2007 <sup>46</sup>	73/M	None/Diabetes mellitus; pulmonary asbestosis	Headache, left-sided visual loss, scalp tenderness, fatigue (3 weeks)	Hypertrophic pachymeningitis	L/Meningeal biopsy	WBC 0/μL; protein 5670 mg/L	<i>Aspergillus flavus</i> (biopsy culture)	ND	Antifungal treatment (NR)	Death 3 months later
1243	Kagawa et al., 2008 <sup>47</sup>	33/F	Spinal cord mass lesion	Headache, low grade fever (5 months), hydrocephalus	Chronic meningitis	L/Biopsy VA shunt	WBC 1340/μL; glucose 8 mg/dL; protein 1580 mg/L	<i>Aspergillus</i> spp. (VA shunt biopsy)	ND	AMFB (NR); fluconazole (NR)	Alive after 15 years (multiple recurrences)
1244	Chan et al., 2011 <sup>48</sup>	59/M	Diabetes; impaired renal function	Headache, diplopia, hoarseness (2 months)	Pachymeningitis	L/Dural biopsy	Glucose 102 mg/dL; protein 1270 mg/L	<i>Aspergillus flavus</i> (culture from dural biopsy)	Positive (β-D-glucan + Platelia)	Voriconazole (2 weeks); caspofungin (4 weeks); voriconazole	Alive after 7 months
1245	Kato et al., 2011 <sup>49</sup>	42/M	None/None	Headache, right nuchal pain, cranial nerve palsies <sup>9,10,11,12</sup> (2 months)	Hypertrophic pachymeningitis	L/CSF	WBC 43/μL (PMNs 4%); glucose 56 mg/dL; protein 1000 mg/L	<i>Aspergillus</i> spp. (CSF PCR positive)	β-D-glucan (Fungitell) 164 pg/mL; serum < 5 pg/mL	Voriconazole (8 weeks); L-AMB + 5-FLU (2 weeks); fluconazole 8 weeks	Alive after 30 months
1246	<b>Meningoencephalitis</b>										
1247	Goldhammer et al., 1974 <sup>50</sup>	45/M	None/none	Headache (9 months), blurred vision (3 weeks)	Meningoencephalitis	Pm/Autopsy (disseminated meningoencephalitis with pituitary abscess and left optic nerve involvement)	ND	<i>Aspergillus</i> spp. (microscopy smear of pituitary abscess + autopsy)	NA	None	Death 4 days postoperatively
1248	Naidoff et al., 1975 <sup>51</sup>	29/F	Kidney transplant/End stage kidney disease	NR	Meningoencephalitis	Pm/Autopsy. disseminated aspergillosis (heart, lung, liver, spleen, thyroid, brain, eye, meninges)	ND	<i>Aspergillus fumigatus</i> (autopsy culture)	NA	None	Death in a few days
1249	Kaufman et al., 1976 <sup>52</sup>	31/F	IVDA (heroin)/none	Headache (9 months), blurred vision (2 months), intermittent diplopia, hearing loss	Meningo-encephalitis	L/Lobectomy; CSF/ Autopsy: granulomatous basilar leptomeningitis; aspergilloma left frontal gyrus; transtentorial and tonsillar herniation	WBC 1150/μL (PMNs 83%); glucose 20 (s 119) mg/dL;	<i>Aspergillus fumigatus</i> (CSF + frontal granuloma culture)	NA	AMFB (2 weeks)	Death after 3 weeks

(continued on next page)

1365	Horton et al., 1976 <sup>53</sup>	17/F	Fungal endocarditis/ aortic stenosis	Headache, incoordination, right-sided numbness, seizure	Meningoencephalitis	Pm/Autopsy: mycotic aneurism of the middle cerebral artery with subarachnoid hemorrhage)	NR	<i>Aspergillus fumigatus</i> NA (CSF culture)	None	Death after 9 days
1366	Galassi et al., 1978 <sup>54</sup>	59/F	Neurosurgery/ Meningioma	Intermittent fever, seizures, aphasia, hemiparesis/12 months	Meningoencephalitis	L/Surgery of dura granulomas; CSF/ Autopsy: diffuse purulent meningo- encephalitis	NR	<i>Aspergillus fumigatus</i> NA (CSF culture)	AMFB (3 months)	Death after 3 months
1367	Peacock et al., 1984 <sup>55</sup>	23/M	Chemotherapy/ Refractory anemia	Fever, headache, lethargia (57 days post-chemo)	Meningoencephalitis	L/Biopsy (pulmonary); Autopsy: ( <i>Aspergillus</i> leptomeningites; necrotizing vasculitis mg/L (pons and basal ganglia); tonsillar herniation; necrotizing pneumonia)	WBC 117-1126/ $\mu$ L (PMNs 88–99%); glucose 13–48 mg/ dL; protein 540–3460 mg/L	<i>Aspergillus terreo</i> (culture lung biopsy); CSF <i>Aspergillus</i> antigen	Positive (RIA) AMFB +5-FLU + rifampicin (NR)	Death after 65 days
1368	Quammou et al., 1986 <sup>56</sup>	3/M	Neurosurgery/  mycetomaAutopsy: encephalitis (cerebral hemispheres, brain stem)	WBC 52/ $\mu$ L (PMNs 70%); glucose 10 mg/ dL; protein 1200 mg/ L; Headache, fever (38.2 °C), confusion, vomiting	Encephalomeningocele  <i>Aspergillus fumigatus</i> (CSFNA)	Fever (37.8 °C), frontal subcutaneous abscess/3 days	Griseofulvin (3 months)	Meningoencephalitis L/CSF; surgery: meningeal	Death after 3 months	
1369	Cox et al., 1990 <sup>57</sup>	31/M	None/AIDS	Headache, fever (38.2 °C), confusion, vomiting	Meningoencephalitis	PM/Autopsy ( <i>Aspergillus</i> meningitis; mycotic aneurysms; endocarditis; myocarditis)	ND	<i>Aspergillus</i> spp. (autopsy histology)	NA	Death after few days
1370	Breneman et al., 1992 <sup>5</sup>	50/M	IVDA; steroid therapy/ COPD	Fever (38.6 °C), dyspnea, headache; stiff neck, progressive mental status change (3 days)	Meningoencephalitis	L/brain biopsy	WBC 4100/ $\mu$ L (PMNs 96%); glucose 33 mg/dL; protein 1340 mg/L	<i>Aspergillus fumigatus</i> NA (Brain biopsy culture)	AMFB (few days)	Death after few days
1371	Van der Knaap et al., 1993 <sup>58</sup>	3/M	None/Galactosemia	Fever (40 °C), nuchal rigidity, convulsions, left hemiparesis	Meningoencephalitis	L/CSF positive antigen	Normal	<i>Aspergillus</i> spp.	Positive (NR)	Improvement
1372	Mikolich et al., 1996 <sup>6</sup>	25/F	None/None	Worsening headache (3 months); vomiting; photophobia (1 month); papilledema	Meningoencephalitis	L/brain biopsy	WBC 200/ $\mu$ L (PMNs 2%); glucose 40 mg/dL; protein 920 mg/L	<i>Aspergillus fumigatus</i> NA (brain biopsy)	Itraconazole (24 months)	Alive after 4 years



1489	Darras-Joly et al., 1996 <sup>23</sup>	17/F	Neurosurgery/ Ependymoma	Fever (40 °C), neck stiffness/7 days after surgery	Meningoencephalitis; ventriculitis	L/Surgical drainage	WBC 1900/μL (PMNs 97%); glucose 36 mg/dL; protein 1100 mg/L	<i>Aspergillus fumigatus</i> Negative (NR) (surgical culture)	AMFB (72 days) + itraconazole (30 days)	Death after 96 days
1490	Schwartz et al., 1997 <sup>59</sup>	18/M	Chemotherapy/ALL	Meningism, fever/ (92 days post- chemotherapy)	Meningoencephalitis	L/brain biopsy	WBC 1056/μL (PMNs 96%)	<i>Aspergillus</i> spp. (BrainND biopsy)	Itraconazole (4 weeks); voriconazole (6 months) ND	Death after 6 months
1491	Koh et al., 1998 <sup>60</sup>	15/F	Chemotherapy/ALL	Flaccid weakness lower extremities, slurred speech, urinary retention	Meningiomeloencephalitis	Pm/Autopsy Multifocal leptomeningeal exudates; fungal abscess/necrosis in spinal cord	ND	<i>Aspergillus</i> spp. (autopsy histology)	ND	Death 21 days later
1492	Payot et al., 1999 <sup>61</sup>	29/M	None/AIDS	Headache (3 weeks), nausea (1 week), fever (39 °C), nuchal rigidity	Meningoencephalitis	Pm/Autopsy ( <i>Aspergillus</i> purulent basal meningitis + bulbar encephalitis)	WBC 19/μL (PMN 50%); protein 1080 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	Death after 7 days
1493	Fasciano et al., 1999 <sup>62</sup>	26/M	Steroid treatment/ Chronic asthma	Fever, quadriplegia, areflexia; hydrocephalus (2 weeks)	Meningoencephalitis	L/Brain biopsy/ Autopsy: Aspergillosis of brain, meninges, cauda equina, bilateral uncus herniation; lungs, thyroid)	WBC 1300/μL (PMNs 98%); glucose 40 mg/dL; protein 1100 mg/L	<i>Aspergillus fumigatus</i> ND (brain biopsy)	AMFB iv and intrathecal + 5-FLU (2 weeks)	Death after 6 weeks
1494	Chandra et al., 2000 <sup>63</sup>	40/F	None/Ethmoid and sphenoid sinusitis	Headache, fever, vomiting (1 week); left proptosis	Meningoencephalitis	L/Brain biopsy	NR	<i>Aspergillus fumigatus</i> ND (biopsy)	NR	NR
1495	Viscoli et al., 2002 <sup>64</sup>	NR	BMT/Acute lymphoblastic leukemia	Fever, neurological deficit, seizures/5 days post-BMT	Meningoencephalitis	Pm/Autopsy (diffuse meningeal and parenchymal infiltration)	NR	<i>Aspergillus</i> spp. (meningeal and parenchymal)	578 (s 25.7) (Platelia)	Death
1496	Wang et al., 2003 <sup>65</sup>	39/M	Steroid treatment/ SARS	Tentorial herniation	Meningoencephalitis	Pm/Autopsy: <i>Aspergillus</i> meningitis; multiple brain abscess containing aspergillus; disseminated aspergillosis heart, kidney, spleen, pancreas, adrenal glands)	ND	<i>Aspergillus</i> spp. (autopsy histology and culture)	ND	Death
1497	Roberts et al., 2004 <sup>66</sup>	71/F	None/Sinusitis	Fever (38.3 °C), severe headache, diplopia, confusion (5 weeks)	Meningoencephalitis	Pm/Autopsy ( <i>Aspergillus</i> granulomatous meningitis; thrombosis of basilar artery)	WBC 286/μL (PMNs 38%); glucose 23 mg/dL (s 99); protein 850 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	ND	Death after 10 days

(continued on next page)

Botturi et al., 2006 <sup>67</sup>	59/F	Steroid treatment/ Sphenoid sinusitis/	Headache, diplopia; bilateral 6th nerve palsy (5 weeks)	Meningoencephalitis	L/Brain biopsy	WBC 920/μL (PMNs 96%); glucose 0 mg/dL; protein 180 mg/L	<i>Aspergillus</i> spp. (biopsy)	ND	AMFB (8 weeks); voriconazole (6 months)	Alive after 23 months
Gabelmann et al., 2007 <sup>68</sup>	43/F	Chemotherapy/AML; sinusitis	NR	Meningoencephalitis	Pm/Autopsy	NR	<i>Aspergillus</i> spp. (autopsy histology)	ND	NR	Death after 41 days
Van de Beek et al., 2008 <sup>36</sup>	62/F	Kidney-pancreas transplant/End stage disease	Headache (6 months), altered consciousness	Meningoencephalitis	L/Autopsy (cerebral aspergillosis)	WBC 286/μL (PMNs 90%); glucose 27 mg/dL; protein 830 mg/L	<i>Aspergillus</i> spp. (autopsy histology)	2.72 (s 0.06) (Platelia)	ABLC	Death after 12 days
<b>Spinal arachnoiditis</b>										
Bryan et al., 1980 <sup>69</sup>	26/M	IVDA (heroin)/None	Headache, nausea, vomiting (weeks), low back pain; hydrocephalus	Spinal arachnoiditis	L/Lumbar biopsy (lesion L3-5)	WBC 1857/μL (PMNs 43%); glucose 6 mg/dL; protein 5170 mg/L	<i>Aspergillus flavus</i> (immunofluorescence on biopsy) (CSF)	NA	AMFB + rifampicin (10 weeks)	Alive after 14 months
Stein et al., 1982 <sup>70</sup>	24/F	IVDA (heroin)/Chronic alcoholism	Low back pain (4 months), left leg weakness, frequent headache fever (38 °C); confusion and signs of meningeal irritation	Spinal arachnoiditis	L/CSF	WBC 62/μL (PMNs 30%); glucose 70 mg/dL; protein 350 mg/L	<i>Aspergillus terreus</i> (2 sCSF cultures) <sup>f</sup>	NA	AMFB (NR)	Death 26 days after laminectomy
Van de Wyngaert et al., 1986 <sup>71</sup>	30/M	None (splinter stuck on his hand)/none	High fever, painful stiffness of spine, headache, photophobia, nausea	Spinal arachnoiditis	L/CSF	WBC 3200/μL (PMNs 90%); glucose 30 mg/dL; protein 1530 mg/L	<i>Aspergillus fumigatus</i> (CSF) precipitin	NA	AMFB (3 months) + rifampin (10 days)+ 5-FLU (3 months)	Alive after 229 days
Endo et al., 2001 <sup>72</sup>	55/M	Neurosurgery/Pituitary adenoma	Diplopia, retro-orbital pain (1 year), loss of vision/9 years	Arachnoiditis; subdural abscess	L/Abscess aspiration	NR	<i>Aspergillus .fumigatus</i> (abscess culture)	ND	AMFB + fluconazole (4 weeks)	Death after 1 month
Genzen et al., 2009 <sup>73</sup>	37/F	Spinal anesthesia (12 months prior pregnancy)	Headache (months); fever (37.4 °C), blurred vision, numbness left lower extremity	Arachnoiditis	L/Laminectomy & tissue biopsy	WBC 970/μL (PMN 92%); glucose 50 mg/dL; protein 1010 mg/L	<i>Aspergillus terreus</i> (biopsy culture)	ND (s 0.47)	Voriconazole (78 days); voriconazole + caspofungin (54 days); AMFB (6 days); ABLC (50 days)	Alive after 9 months
<b>Ventriculitis</b>										
Morrow et al., 1983 <sup>4</sup>	36/M	IVDA (heroin)/None	Fever, generalized seizures, nuchal rigidity (1 day)	Ventriculitis	Pm/Autopsy (ventriculitis & hydrocephalus)	WBC 549/μL (PMNs 27%); glucose 29 mg/dl; protein 1200 mg/L	<i>Aspergillus flavus</i> (serology) <sup>h</sup>	NA	None	Death after 40 days
Hummel et al., 2006 <sup>74</sup>	4/F	Chemotherapy/ALL	NR	Ventriculitis & multiple abscess	L/CSF (Ommaya reservoir)	NR	<i>Aspergillus fumigatus</i> (PCR CSF)	Positive (Platelia)	Voriconazole + caspofungin (5 weeks); intraventricular AMFB (4 weeks); voriconazole (2 months)	Alive after 3 months

Please cite this article in press as: Antinori S, et al., *Aspergillus meningitis: A rare clinical manifestation of central nervous system aspergillosis*. Case report and review of 92 cases, J Infect (2012), <http://dx.doi.org/10.1016/j.jinf.2012.11.003>

Q2

Sutton et al., 2009 <sup>75</sup>	18/M	Lung transplant/End stage pulmonary disease	Headache, seizure, low grade fever, altered mental status	Ventriculitis	Pm/Autopsy (necrotizing granulomatous inflammation of meninges)	WBC 1100/μL (PMNAspergillus granulosis ND 79%); glucose 41 mg/dL (s 122); protein 1090 mg/L	Death after 87 days
Antachopoulos et al., 2011 <sup>76</sup>	5/F	VP shunt	Fever (40 °C), tonic/clonic seizures	Ventriculitis	L/VP	WBC 400/μL (Neutrophil predominance); glucose 25 mg/dL (s 110 mg/dL); protein 1000 mg/L	Death after 9 months
<p>M = male; F = female; IVDA = intravenous drug abuser; CSF = cerebrospinal fluid; L = life; Pm = post-mortem; Ag GMN = galactomannan antigen; s = serum; WBC = white blood cells; PMNs = polymorphonuclear; NA = not available; ND = not done; NR = not reported; AMB = amphotericin B deoxycholate; 5FLU = 5-fluorocytosine; L-AMB = liposomal amphotericin B; ABLC = amphotericin B lipid complex; ALL = acute lymphoblastic leukaemia; CML = chronic myelocytic leukaemia; RAEB = refractory anemia with excess blasts; C4def = hereditary complete C4 deficiency; PR = present report.</p> <p>a One of these four patients had meningism and headache.</p> <p>b Reported also in reference <sup>77</sup> (updated the follow-up).</p> <p>c Symptoms appeared 2–21 days after spinal anaesthesia (mean 7.8 days).</p> <p>d Random values of blood glucose were reported.</p> <p>e Reported also in reference <sup>78</sup>.</p> <p>f Discarded as contaminant.</p> <p>g Reported also in reference <sup>79</sup> (updated the follow-up).</p> <p>h Serological speciation made a result compatible with <i>A. flavus</i>.</p>							

with response to therapy. 1-3-β-D-glucan was evaluated in 2 patients with positive results in both. CSF pleocytosis was detected in 61/64 (95.3%) of available specimens with a median cell count of 678/μL and with a neutrophil predominance in 68.4% of cases. Hypoglycorrhachia was shown to be present in 62.5% of cases with a median glucose level of 32.5 mg/dL.

Fifty-six patients received antifungal therapy : amphotericin B deoxycholate (AMFB) alone or associated with 5-fluorocytosine (11 pts), rifampicin (5 pts), itraconazole (3 pts) or fluconazole (1pt) was used in 36 cases; liposomal amphotericin B (L-AMB) was employed in the treatment of 6 individuals; fluconazole was used in five patients (in three patients as the only drug). Two patients received 5-fluorocytosine, alone in one case and with miconazole and fluconazole in the other case. Fifteen patients received voriconazole (in three cases associated with caspofungin), and in 4 following AMFB use. AMFB was the main antifungal employed until 1996 when oral itraconazole was used for the first time. Voriconazole and L-AMB were used for the first time in 1997, whereas caspofungin in 2006.

Of those patients who had received at least one dose of antifungal agent, 30 (51.7%) died after an interval of time ranging from few days up to 6 years. All patients with a chronic meningitis were initially treated with antibiotics and 6 had also received anti-tubercular therapy. An overall case-fatality rate (CFR) of 72.1% was observed, with significant differences between immunocompetent patients (63.5%) as opposed to immunocompromised patients (82.9%).

Autopsy was available in 49 cases and it was the method by which diagnosis was made for 40 patients (81.6%). In twelve cases basilar meningitis was identified; spinal cord involvement was observed in 5 patients; the presence of a mycotic aneurism involving either the internal carotid artery or the basilar artery was shown in 12 patients with concomitant subarachnoid hemorrhage. Transtentorial, tonsillar or uncal herniation was present in three patients.

## Discussion

In a 1969 review of the literature, Mukoyama et al., reported 33 cases of aspergillosis involving the CNS of whom 10 had meningitis and 3 had meningoencephalitis. However, *Aspergillus* isolation failed in all 10 cultured cerebrospinal fluid specimens.<sup>7</sup>

In a clinical-pathological study of central nervous system aspergillosis only 1 patient had signs of meningeal irritation during life while at autopsy the meninges were focally affected in nearly half of the cases.<sup>8</sup>

In the present series regarding 93 patients, a picture of pure meningitis was observed in 65.6% of cases,<sup>3,8–22,24–49</sup> while meningoencephalitis was diagnosed in about 25% of patients.<sup>5,6,36,50–68</sup>

In patients with a diagnosis of meningitis fever and headache were the most common presenting symptoms (78.8%) followed by neck stiffness in 28.2% (24/85).<sup>3–6,9–76</sup> However, only 16.5% (14/85) of patients presented with three of the four signs and symptoms of headache, fever, neck stiffness and altered mental status.<sup>5,10,18–20,25,33–36,40,57,61,66,70</sup> Cranial nerve palsies were

**Table 2** Characteristics of patients with aspergillus meningitis.

	Immunocompetent patients, <i>n</i> = 52 (%)	Immunocompromised patients, <i>n</i> = 41 (%)	Total, <i>n</i> = 93 (%)
Age, years median (range)	34.5 (3–73)	39 (4–75)	37 (3–75)
Sex, female (%)	34 (65.4)	15/40 (37.5)	49/92 (53.3)
Diagnosis during life	36/52 (69.2)	16/41 (39)	52/93 (55.9)
Death after diagnosis in life	18/36 (50.0)	9/16 (56.3)	27/54 (50.0)
Total deaths	33/52 (63.5)	34/41 (82.9)	67/93 (72.1)
Clinical picture			
Meningitis	27 (51.9) <sup>a</sup>	19 (46.3)	46 (49.5)
Meningoencephalitis	10 (19.2)	13 (31.7)	23 (24.7)
Chronic meningitis/pachymeningitis	8 (15.4) <sup>b</sup>	7 (17.1)	15 (16.1)
Spinal arachnoiditis	5 (9.6) <sup>c</sup>	–(0.0)	5 (5.4)
Ventriculitis	2 (3.8)	2 (4.9) <sup>d</sup>	4 (4.3)
CSF characteristics			
Positive culture	17/46 (36.9)	4/22 (18.2)	21/68 (30.9)
Positive PCR	3/3 (100)	3/3 (100)	6/6 (100)
Median WBCs/μL (range)	640 (5–8800)	988 (0–4100)	678 (0–8800)
Neutrophils predominance (≥60%)	25/37 (67.6)	14/20 (70)	39/57 (68.4)
Hypoglycorrachia	9/14 (64.3)	1/2 (50)	10/16 (62.5)
Median glucose level (mg/dL)	30 (1–77)	33 (0–102)	32.5 (0–102)
Glucose ≤ 25 mg/dL	16/39 (41.1)	4/17 (23.5)	20/56 (35.7)
Median protein level (range) (mg/L)	995 (100–7900)	1090 (180–7300)	1007 (100–7900)
Median galactomannan antigen (range)	7.05 (5.5–10.4)	4.58 (2.2–578)	6.58 (2.2–578)
Positive	6/8 (75)	7/7 (100)	13/15 (86.7)

<sup>a</sup> 1 patient also had empyema, 1 abscess, 1 spinal arachnoiditis.

<sup>b</sup> 1 patient had concomitant ventriculitis + arachnoiditis.

<sup>c</sup> 1 patient had concomitant subdural abscess.

<sup>d</sup> 1 patient had concomitant multiple abscess.

reported in 17.6% (15/85) and seizures (11/86) in 12.8% of patients.

The diagnosis of *Aspergillus* meningitis is very difficult and challenging. In fact, a diagnosis during life was obtained only in 55.9% of patients although with a much higher frequency among immunocompetent patients (69.2%)<sup>3,6,10,12,13,15,22,23,25–27,29,32,33,39,44,45,47,52,54,56,58,63,69–73,76,78,79</sup> PR as opposed to immunocompromised individuals (39%).<sup>5,9,28,29,34,36,40,42,46,48,55,59,74</sup> This difference might be explained by a more aggressive and acute course of the disease observed in immunosuppressed hosts. A culture-based diagnosis of *Aspergillus* meningitis is hampered by the lack of sensitivity as shown by the 31% of positive results observed in our review of published cases.<sup>3,9,13,22,23,25,26,29,33,35,37,40,45,52–54,56,70</sup> PR It has been previously suggested that a minimum of 5 mL of cerebrospinal fluid should be cultured when a mycosis is suspected or that repeated culture of large volumes of CSF are critical for successful *in vitro* isolation. However, such large volumes are not easy to obtain in clinical practice.<sup>80</sup> On the other hand, serial lumbar puncture does indeed seem to have a role since in 9 cases, the fungus could be successfully isolated from cerebrospinal fluid only after several attempts.<sup>3,25,26,29,35,37,40,45</sup>

Non-culture based diagnostic methods for the diagnosis of aspergillosis were employed on CSF in fifteen patients and seem to outperform traditional culture, with a overall sensitivity of 87%.<sup>23,25,28,29,34,36,48,49,64,75,76</sup> PR Although a cut-off value of the GM index has not yet been formally

established for the diagnosis of CNS aspergillosis, it has been proposed that it might be lower than that used for serum samples due to the lower back-ground reactivity of CSF.<sup>25,81</sup>

The median CSF GM index in this series was 6.58 which is a value higher than what is usually observed in serum and well above the cut-off of 0.5 when two serial serum determinations are used among immunocompromised patients or the 0.7–1 value when a single determination is employed in non-hematological patients.<sup>82,83</sup> Notably, when both serum and CSF GM were screened concomitantly, negative results were observed in three cases in serum and the index value was always higher in CSF than in serum.<sup>29,34,36,64</sup> PR Although serial determinations on CSF were available only in three cases they may provide useful information on the therapeutic response.<sup>25,29</sup> PR Finally, it seems that the Platelia GM test works well irrespective of the species of *Aspergillus* involved as shown by the cases described by Verveij, Moling and ourselves in whom *A. fumigatus*, *A. candidus* and *A. flavus* were respectively cultured from the CSF.<sup>25,29</sup> PR

Our review shows that *Aspergillus* meningitis has an ominous prognosis with a global case-fatality rate (CFR) of 72.1% but with a much better outcome among immunocompetent patients in whom a CFR of 63.5% was observed versus a 83% CFR registered among immunocompromised patients. Our data are only slightly better than the 88% CFR reported by Lin et al. in a literature-based survey published before 2001.<sup>84</sup>



The Infectious Diseases Society of America (IDSA) guidelines recommend voriconazole for the treatment of central nervous system aspergillosis but these recommendations are mainly based upon studies regarding patients with hematological disorders and there is no specific mention as to the treatment of *Aspergillus* meningitis.<sup>85</sup> In our present review, that encompasses a long period of time before the introduction of voriconazole (i.e., 2002), most patients (64.3%) were treated with amphotericin B deoxycholate and less than 30% received voriconazole at some time of their disease.<sup>32,33,34,36,48,49,67,73–76</sup> PR In a recent analysis conducted by Schwartz et al. on 120 cases of CNS aspergillosis a 47% response rate and a median survival of 159 days among patients treated with voriconazole was shown.<sup>86</sup> Voriconazole shows excellent penetration into the CNS as demonstrated by studies conducted in healthy guinea pigs in whom high cerebrospinal fluid to plasma ratio (0.68) together with rapid penetration across the blood brain barrier were observed.<sup>87</sup> Including the present report, determination of cerebrospinal fluid concentrations of voriconazole were available in four cases, with reported values ranging from 0.8 to 5.86 mg/L and with a CSF/plasma ratio ranging from 38% to 76 %.<sup>25,59PR</sup> Hope recently proposed that in the busy clinical setting, voriconazole therapeutic drug monitoring (TDM) should be obtained at the end of day 2 and subsequently in the first week of therapy.<sup>88</sup> An association between poor outcome and voriconazole concentrations has been initially observed by Pascual and coworkers.<sup>89</sup> In addition Miyakis et al. recently showed an 11-fold increased risk of death among patients with invasive mycoses treated with voriconazole who had an initial trough concentration of less than 0.35 mg/L.<sup>90</sup> By contrast, several studies and expert opinion suggest that the optimal maximum voriconazole concentrations should not exceed 5.5–5.8 mg/L.<sup>89,91,92</sup>

Another crucial issue not yet addressed so far is the optimal length of antifungal therapy in patients with *Aspergillus* meningitis, as well as for cerebral aspergillosis. In our patient, antifungal treatment was administered for 7 months, 5 of which employing voriconazole but, just before losing the patient to follow-up we were uncertain how long it would have been necessary to continue the specific treatment. Our analysis of the literature regarding patients with *Aspergillus* meningitis who were treated with voriconazole shows very different lengths of treatment, ranging from 8–14 weeks to 5–12 months.<sup>25,32–34,67,74,76PR</sup>

However, it should be pointed out that in most cases, the outcome following drug discontinuation is not reported. The long term duration of voriconazole treatment for patients with *Aspergillus* meningitis or with CNS involvement is a matter not only of efficacy but also of toxicity. In this regard, the risk of phototoxicity and, above all, the risk of inducing squamous cell carcinoma should be mentioned.<sup>93</sup>

Caspofungin was employed in 5 patients, (in 4 of whom in combination with voriconazole), but its role, if there is any, as a single agent in the treatment of aspergillus meningitis is hampered by the lack of significant penetration across the blood–brain barrier of this drug.<sup>94</sup> Except one apparently successful case, flucytosine has been used only in association with AMFB and its role in the treatment of aspergillosis remains anecdotal.<sup>9,95</sup>

In conclusion, our review shows that *Aspergillus* meningitis is a rare clinical entity that is much more frequently

observed among immunocompetent patients. It is characterized by CSF neutrophil pleocytosis in 68% of cases and hypoglycorrhachia in 62% of cases. Cultures of CSF are positive only in one third of cases, but the GM antigen test is very useful, with a sensitivity reaching 87%. Although our data show a poor prognosis, we believe that the more widespread use of diagnostic methods with greater sensitivity (i.e., PCR and GM), together with the availability of voriconazole therapy, may allow improved outcomes provided that the diagnosis is achieved earlier. The optimal length of antifungal therapy however remains to be determined.

## Funding

No particular funding was received to support this work.

## Conflict of interest

Spinello Antinori none Mario Corbellino none Luca Meroni none Federico Resta none Salvatore Sollima none Massimo Tonolini none Anna Maria Tortorano none Laura Milazzo none Lorenzo Bello none Elisa Furfaro none Massimo Galli none Claudio Viscoli none.

## Acknowledgments

We thank Rosamaria Rotolo, Virginia Zanzottera, and Rossella Garlaschelli of the Biblioteca "Alberto Malliani" of the University of Milano for their excellent help to retrieve much of the articles.

## References

- Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. *Rev Infect Dis* 1990;12:1147–201.
- Denning DW. Therapeutic outcome of invasive aspergillosis. *Clin Infect Dis* 1996;23:608–15.
- Gordon MA, Holzman RS. *Aspergillus oryzae* meningitis. *JAMA* 1976;235:2122–3.
- Morrow R, Wong B, Finkelstein WE, Sternberg SS, Armstrong D. Aspergillosis of the cerebral ventricles in a heroin abuser. *Arch Intern Med* 1983;143:161–4.
- Breneman E, Colford Jr JM. Aspergillosis of the CNS presenting as aseptic meningitis. *Clin Infect Dis* 1992;15:737–8.
- Mikolich DJ, Kinsella LJ, Skowron G, Friedman J, Sugar AM. *Aspergillus* meningitis in an immunocompetent adult successfully treated with itraconazole. *Clin Infect Dis* 1996;23:1318–9.
- Mukoyama M, Gimple K, Poser CM. Aspergillosis of the central nervous system. Report of a brain abscess due to *A. fumigatus* and review of the literature. *Neurology* 1969;19:967–74.
- Walsh TJ, Hier DB, Caplan LR. Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. *Ann Neurol* 1985;18:574–82.
- Atkinson GW, Israel HL. 5-fluorocytosine treatment of meningeal and pulmonary aspergillosis. *Am J Med* 1973;55:496–504.
- Feely M, Steinberg M. *Aspergillus* infection complicating transphenoidal yttrium-90 pituitary implant. *J Neurosurg* 1976;46:530–2.
- Mohandas S, Ahuja GK, Sood VP, Virmani V. Aspergillosis of the central nervous system. *J Neurol Sci* 1978;38:229–33.

12. Aung BUK, Lin UK, Nyunt US. Leptomeningeal aspergillosis causing internal carotid artery stenosis. *B J Radiol* 1979;52:328–9.
13. Beal MF, O'Carroll PC, Kleinmann GM, Grossman RI. Aspergillosis of the nervous system. *Neurology* 1982;32:473–9.
14. Diendogh JV, Barnard RO, Thomas DGT. Aspergillosis of the nervous system. Report of two cases. *Neuropathol Appl Neurobiol* 1983;9:477–84.
15. Hajjar J, Brunon J, Jaubert J, Aubert G, Duthel R, Delorme C, et al. Cerebral aspergillosis. Report on four cases. *Neurochirurgie* 1987;33:142–7.
16. Asnis DS, Chitkara RK, Jacobson M, Goldenstein JA. Invasive aspergillosis: an unusual manifestation of AIDS. *NY State J Med* 1988;88:653–5.
17. Carrazana EJ, Rossitch Jr E, Morris J. Isolated central nervous system aspergillosis in the acquired immunodeficiency syndrome. *Clin Neurol Neurosurg* 1991;93:227–30.
18. Komatsu Y, Narushima K, Kobayashi E, Tomono Y, Nose T. *Aspergillus* mycotic aneurysm-case report. *Neurol Med Chir (Tokyo)* 1991;31:346–50.
19. Lammens M, Robberecht W, Waer M, Carton H, Dom R. Purulent meningitis due to aspergillosis in a patient with systemic lupus erythematosus. *Clin Neurol Neurosurg* 1992;94:39–43.
20. Torre-Cisneros J, Lopez OL, Kusne S, Julio Martinez A, Starzl TE, Simmons RL, et al. CNS aspergillosis in organ transplantation: a clinicopathological study. *J Neurol Neurosurg Psychiatr* 1993;56:188–93.
21. Miaux Y, Ribaud P, Williams M, Guermazi A, Gluckman E, Brocheriou C, et al. MR of cerebral aspergillosis in patients who have had bone marrow transplantation. *Am J Neuroradiol* 1995;16:552–62.
22. Adunsky A, Rubinstein E, Goldsmith A. *Aspergillus flavus* meningitis and pontine hemorrhage in an older patient. *J Amer Geriatr Soc* 1996;44:739–40.
23. Darras-Joly C, Veber B, Bedos JP, Gachot B, Regnier B, Wolff M. Nosocomial cerebral aspergillosis: a report of 3 cases. *Scand J Infect Dis* 1996;28:317–9.
24. Monlun E, De Blay F, Berton C, Gasser B, Jaeger A, Pauli G. Invasive pulmonary aspergillosis with cerebromeningeal involvement after short-term intravenous corticosteroid therapy in a patient with asthma. *Respir Med* 1997;91:435–7.
25. Verweij PE, Brinkman K, Kremer HPH, Kullberg B-J, Meis JFGM. *Aspergillus* meningitis: diagnosis by non-culture-based microbiological methods and management. *J Clin Microbiol* 1999;37:1186–9.
26. Mariushi WM, Arruda WO, Tsubouchi ME, Ramina R. Chronic *Aspergillus* sp. Meningitis successfully treated with fluconazole. *Arq Neuropsiquiatr* 1999;57:288–91.
27. Arabi Y. Nosocomial meningoencephalitis in medical patients. *Internet J Infect Dis* 2001;1:2.
28. Nenoff P, Kellermann S, Horn L-C, Keiner S, Bootz F, Schneider S, et al. Mycotic arteritis due to *Aspergillus fumigatus* in a diabetic with retrobulbar aspergillosis and mycotic meningitis. *Mycoses* 2001;44:407–14.
29. Moling O, Lass-Floerl C, Verweij PE, Porte M, Prugger M, Gebert U, et al. Chronic and acute *Aspergillus* meningitis. *Mycoses* 2002;45:504–11.
30. Kleinschmidt-DeMasters BK. Central nervous system aspergillosis: a 20-year retrospective series. *Hum Pathol* 2002;33:116–24.
31. Pandian JD, Sarada C, Radhakrishnan VV, Kishore A. Iatrogenic meningitis after lumbar puncture- a preventable health hazard. *J Hosp Infect* 2004;56:119–24.
32. Larson Kolbe AB, McKinsey AM, Tuba Karagulle Kendi A, Misselt D. *Aspergillus* meningitis and discitis from low-back procedures in an immunocompetent patient. *Acta Radiol* 2007;6:687–9.
33. Gunaratne PS, Wijeyaratne CN, Seneviratne HR. *Aspergillus* meningitis in Sri-Lanka- A post-tsunami effect? *N Engl J Med* 2007;356:754–6.
34. Saitoh T, Matsushima T, Shimizu H, Yokohama A, Irisawa H, Handa H, et al. Successful treatment with voriconazole of *Aspergillus* meningitis in a patient with acute myeloid leukemia. *Ann Hematol* 2007;86:697–8.
35. Sundaram C, Goel D, Uppin SG, Seethajayalakshmi S, Borgohain R. Intracranial mycotic aneurism due to *Aspergillus* spp. *J Clin Neurosci* 2007;14:882–6.
36. van de Beek D, Patel R, Campeau NG, Badley A, Parisi JE, Rabistein AA, et al. Insidious sinusitis leading to catastrophic cerebral aspergillosis in transplant recipients. *Neurology* 2008;70:2411–3.
37. Palo J, Haltia M, Uutela T. Cerebral aspergillosis with special reference to cerebrospinal fluid findings. *Eur Neurol* 1975;13:224–31.
38. Mielke B, Weir B, Oldring D, von Westarp C. Fungal aneurysm: case report and review of the literature. *Neurosurgery* 1981;9:578–82.
39. Weinstein JM, Sattler FA, Towfigh J. Optic neuropathy and paratrigeminal syndrome due to *Aspergillus fumigatus*. *Arch Neurol* 1982;39:582–5.
40. Salaki JS, Louria DB, Chmel H. Fungal and yeast infections of the central nervous system. *Medicine* 1984;63:108–32.
41. Woods GL, Goldsmith JC. *Aspergillus* infection of the central nervous system in patients with acquired immunodeficiency syndrome. *Arch Neurol* 1990;47:181–4.
42. Murai H, Kira J, Kobayashi T, Goto I, Inoue H, Hasuo K. Hypertrophic cranial pachymeningitis due to *Aspergillus flavus*. *Clin Neurol Neurosurg* 1992;94:247–50.
43. Kurino M, Kuratsu J, Yamaguchi T, Ushio Y. Mycotic aneurism accompanied by aspergillotic granuloma: a case report. *Surg Neurol* 1994;42:160–4.
44. Mochizuki M, Murase S, Takahashi K, Shimada S, Kume H, Iizuka T, et al. Serum itraconazole and hydroxyitraconazole concentration and interaction with digoxin in a case of chronic hypertrophic pachymeningitis caused by *Aspergillus flavus*. *Jpn J Med Mycol* 2000;41:33–9.
45. Kowacs PA, Manteiro de Almeida S, Pinheiro RL, Fameli H, Piovesan EJ, Correia A, et al. Central nervous system *Aspergillus fumigatus* infection after near drowning. *J Clin Pathol* 2004;57:202–4.
46. Ismail AR, Clifford L, Meacock WR. Compressive optic neuropathy in fungal hypertrophic cranial pachymeningitis. *Eye* 2007;21:568–9.
47. Kagawa R, Okada Y, Moritake K. Fungal meningitic hydrocephalus with repeated shunt malfunction-case report. *Neurol Med Chir* 2008;48:43–6.
48. Chan HS, Yuen HY, Ng WK, Vlantis AC, Ahuja AT, Tong CFM, et al. *Aspergillus* pachymeningitis mimicking nasopharyngeal carcinoma. *J Laryngol Otol* 2011;125:103–7.
49. Kato H, Nakajima M, Ichikawa H, Kawamura M. Hypertrophic pachymeningitis in an immunocompetent adult with positive *Aspergillus* DNA in the cerebrospinal fluid. *Neurol India* 2011;59:111–3.
50. Golhammer Y, Lawton Smith J, Yates BM. Mycotic intrasellar abscess. *Tr Am Ophth Soc* 1974;77:65–78.
51. Naidoff MA, Green WR. Endogenous *Aspergillus* endophthalmitis occurring after kidney transplant. *Am J Ophthalmol* 1975;79:502–9.
52. Kaufman DM, Thal LJ, Framer PM. Central nervous system aspergillosis in two young adults. *Neurology* 1976;26:484–8.
53. Horton BC, Abbott GF, Porro RS. Fungal aneurysms of intracranial vessels. *Arch Neurol* 1976;33:577–9.
54. Galassi E, Pozzati E, Poppi M, Vinci A. Cerebral aspergillosis following intracranial surgery. *J Neurosurg* 1978;49:308–11.
55. Peacock Jr JE, McGinnis MR, Cohen MS. Persistent neutrophilic meningitis. Report of four cases and review of the literature. *Medicine* 1984;63:379–95.
56. Ouamou A, El Ouarzazi A, Belghamdi M, El Faidouzi M. Cerebral aspergillosis and encephalomeningocele. *Child's Nerv Syst* 1986;2:216–8.

57. Cox JN, di Dio F, Pizzolato GP, Lerch R, Pochon N. *Aspergillus* endocarditis and myocarditis in a patient with the acquired immunodeficiency syndrome (AIDS). *Virchows Archiv A Pathol Anat* 1990;**417**:255–9.
58. van der Knaap MS, Valk J, Jansen GH, Kappelle LJ, van Nieuwenhuizen O. Mycotic encephalitis: predilection for grey matter. *Neuroradiology* 1993;**35**:567–72.
59. Schwartz S, Milatovic D, Thiel E. Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukemia. *B J Haematol* 1997;**97**:663–5.
60. Koh S, Ross LA, Gilles FH, Nelson Jr MD, Mitchell WG. Myelopathy resulting from invasive aspergillosis. *Pediatr Neurol* 1998;**19**:135–8.
61. Payot A, Garbino J, Burkhardt K, Delavelle J, Pizzolato G, Kaiser L. Primary central nervous system aspergillosis: a case report and review of the literature. *Clin Microbiol Infect* 1999;**5**: 573–6.
62. Fasciano JW, Ripple MG, Suarez JI, Bhardwaj A. Central nervous system aspergillosis: a case report and literature review. *Hosp Physician* 1999;**4**:63–70.
63. Chandra S, Goyal M, Mishra NK, Gaikwad SB. Invasive aspergillosis presenting as a cavernous sinus mass in immunocompetent individuals: report of three cases. *Neuroradiology* 2000;**42**:108–11.
64. Viscoli C, Machetti M, Gazzola P, De Maria A, Paola D, Van Lint MT, et al. *Aspergillus* galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *J Clin Microbiol* 2002;**40**:1496–9.
65. Wang H, Ding Y, Yang L, Zhang W, Kang W. Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. *N Engl J Med* 2003;**349**:507–8.
66. Roberts M, Carmichael A, Martin P. Cerebral vasculitis caused by *Aspergillus* species in an immunocompetent adult. *Infection* 2004;**32**:360–3.
67. Botturi A, Salmaggi A, Pollo B, Lamperti E, Erbetta A, Boiardi A. Meningitis following relapsing painful ophthalmoplegia in aspergillus sphenoidal sinusitis: a case report. *Neurol Sci* 2006;**27**:284–7.
68. Gabelmann A, Klein S, Kern W, Kruger S, Brambs H-J, Rieber-Brambs A, et al. Relevant imaging findings of cerebral aspergillosis on MRI: a retrospective case-based study in immunocompromised patients. *Eur J Neurol* 2007;**14**:548–55.
69. Bryan CS, Di Salvo AF, Huffman LJ, Kaplan W, Kaufman L. Communicating hydrocephalus caused by *Aspergillus flavus*. *SMJ* 1980;**73**:1641–4.
70. Stein SC, Corrado ML, Friedlander M, Farmer P. Chronic mycotic meningitis with spinal involvement (arachnoiditis): a report of five cases. *Ann Neurol* 1982;**11**:519–24.
71. van de Wyngaert FA, Sindle CJM, Rousseau JJ, Fernandes Xavier FG, Bruche JM, Laterre EC. Spinal arachnoiditis due to *Aspergillus* meningitis in a previously healthy patient. *J Neurol* 1986;**233**:41–3.
72. Endo T, Numagami Y, Jokura H, Ikeda H, Shirane R, Yoshimoto T. *Aspergillus* parasellar abscess mimicking radiation-induced neuropathy. Case report. *Surg Neurol* 2001;**56**:195–200.
73. Genzen JR, Kenney B. Central nervous system *Aspergillus* infection after epidural analgesia: diagnosis, therapeutic challenges, and literature review. *Diagn Microbiol Infect Dis* 2009;**65**:312–8.
74. Hummel M, Spiess B, Kentouche K, Niggemann S, Bohm C, Reuter S, et al. Detection of *Aspergillus* DNA in cerebrospinal fluid from patients with cerebral aspergillosis by a nested PCR assay. *J Clin Microbiol* 2006;**44**:3989–93.
75. Sutton DA, Wickes BL, Romanelli AM, Rinaldi MG, Thompson EH, Fothergill AW, et al. Cerebral aspergillosis caused by *Aspergillus* granulosis. *J Clin Microbiol* 2009;**47**:3386–90.
76. Antachopoulos C, Stergiopoulou T, Simitsopoulou M, Georgiadou E, Kottas S, Marinopoulos D, et al. Ventriculitis caused by *Aspergillus fumigatus* in a child with central nervous system tuberculosis. *Mycoses* 2011;**54**:e627–30.
77. Falkeis C, Mark W, Sergi C, Heininger D, Neumair F, Scheiring J, et al. Kidney transplantation in patients suffering from hereditary complete complement C4 deficiency. *Transplant Int* 2007;**20**:1044–9.
78. Rodrigo N, Perera KNT, Ranwala R, Jayasinghe S, Warnakulasurya A, Hapuarachchi S. *Aspergillus* meningitis following spinal anesthesia for caesarean section in Colombo, Sri Lanka. *Int J Obs Anesth* 2007;**16**:256–60.
79. Stenson S, Brookner A, Rosenthal S. Bilateral endogenous necrotizing scleritis due to *Aspergillus oryzae*. *Ann Ophthalmol* 1982;**14**:67–72.
80. McGinnis MR. Detection of fungi in cerebrospinal fluid. *Am J Med* 1983;**75**(1B):129–38.
81. Klont RR, Mennik-Kertsen MA, Verveij PE. Utility of *Aspergillus* antigen detection in specimens other than serum specimens. *Clin Infect Dis* 2004;**39**:1467–74.
82. Maertens JA, Klont R, Masson C, Theunissen K, Meersseman W, Lagrou K, et al. Optimization of the cut-off for the *Aspergillus* double-sandwich enzyme immunoassay. *Clin Infect Dis* 2007;**44**:1329–36.
83. Guinea J, Jensen J, Pelaez T, Gijón P, Alonso R, Rivera M, et al. Value of a single galactomannan determination (Platelia) for the diagnosis of invasive aspergillosis in non-hematological patients with clinical isolation of *Aspergillus* spp. *Med Mycol* 2008;**46**:575–9.
84. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001;**32**:358–66.
85. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;**46**:327–60.
86. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. *Infection* 2011;**39**:201–10.
87. Lutsar I, Roffey S, Troke P. Voriconazole concentrations in the cerebrospinal fluid and brain tissue in guinea pigs and immunocompromised patients. *Clin Infect Dis* 2003;**37**:728–32.
88. Hope WW. Population pharmacokinetics of voriconazole in adults. *Antimicrob Agents Chemother* 2012;**56**:526–31.
89. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* 2008;**46**:201–11.
90. Miyakis S, van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. *Clin Microbiol Infect* 2010;**16**:927–33.
91. Kim S-H, Yim D-S, Choi S-M, Kwon JC, Han S, Lee DG, et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. *Int J Infect Dis* 2011;**15**:e753–8.
92. Pasqualotto AC, Xavier MO, Andreolla HF, Linden R. Voriconazole therapeutic drug monitoring: focus on safety. *Expert Opin Drug Saf* 2010;**9**:125–37.
93. Epaulard O, Leccia M-T, Blanche S, Chosidow O, Mamzer-Bruneel MF, Ravaud P, et al. Phototoxicity and photocarcinogenesis associated with voriconazole. *Med Mal Infect* 2011;**41**:639–45.
94. Bellmann R. Clinical pharmacokinetics of systemically administered antimycotics. *Curr Clin Pharmacol* 2007;**2**:37–58.
95. Polak AM, Scholer HJ, Wall M. Combination therapy of experimental candidiasis, cryptococcosis, and aspergillosis in mice. *Chemotherapy* 1982;**28**:461–79.